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1: Gabellini N. Related Articles, Links

Transcriptional regulation by cAMP and Ca2+ links the na+/ca2+ exchanger 3 to memory and sensory pathways.
Mol Neurobiol. 2004 Aug;30(1):91-116.
PMID: 15247490 [PubMed - in process]

2: Gabellini N, Bortoluzzi S, Danieli GA, Carafoli E. Related Articles, Links

Control of the Na+/Ca2+ exchanger 3 promoter by cyclic adenosine monophosphate and Ca2+ in differentiating neurons.
J Neurochem. 2003 Jan;84(2):282-93.
PMID: 12558991 [PubMed - indexed for MEDLINE]

3: Gabellini N, Bortoluzzi S, Danieli GA, Carafoli E. Related Articles, Links

The gene promoter of human Na+/Ca2+ exchanger isoform 3 (SLC8A3) is controlled by cAMP and calcium.
Ann N Y Acad Sci. 2002 Nov;976:282-4. No abstract available.
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4: Gabellini N, Bortoluzzi S, Danieli GA, Carafoli E. Related Articles, Links

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The human SLC8A3 gene and the tissue-specific Na+/Ca2+ exchanger 3 isoforms.

Gabellini N, Bortoluzzi S, Danieli GA, Carafoli E.

Department of Biological Chemistry, University of Padova, Via G. Colombo, 3, 35121 Padua, Italy. nadia.gabellini@unipd.it

We have identified the human gene for member 3 of Solute Carrier family 8 (SLC8A3) by bioinformatic analysis of human genomic sequences. The gene is located on chromosome 14q24.2, and spans a region of about 150 kb. The full-length DNA complementary to RNA encoding the Na(+)/Ca(2+) exchanger isoform 3 (NCX3), amplified by reverse transcriptase-polymerase chain reaction (RT-PCR) from the human neuroblastoma SH-SY5Y RNA, includes seven exons and encodes a protein of about 100 kDa. RT-PCR analysis was performed in different tissues to determine the exon composition in the region encoding the large intracellular loop of the protein. The region underwent modifications by alternative tissue-specific splicing. NCX3.2, including exon 4 but not exon 5, was found in human brain and in the neuroblastoma cell line. In human skeletal muscle two additional isoforms were identified: NCX3.3, including exons 4 and 5, and a truncated isoform (NCX3.4) produced by the skipping of both exons 3 and 4. The skipping causes a frame shift downstream of the exon 2 sequence. The new coding sequence of 25 amino acids terminates with a stop codon in exon 6. The NCX3.4 isoform (68 kDa) is truncated in the C-terminal portion of the domain first found in Drosophila Na(+)/Ca(2+) exchanger domain (Calxbeta) and lacks the C-terminal hydrophobic segments.

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The human gene for member 3 of solute carrier family 8 (SLC8A3), encoding the Na+/Ca2+ exchanger isoform 3 (NCX3), was identified on chromosome 14q24.2. The minimal promoter region was predicted 250 bp upstream of exon 1. This was confirmed by luciferase reporter assays of pGL3-promoter constructs in transfected SH-SY5Y cells. The promoter activity was monitored during the differentiation of this cell line elicited by the sequential treatment with retinoic acid and brain-derived neurotrophic factor (BDNF). The activity was induced by cyclic AMP (cAMP) via the CRE (cAMP response element) and was stimulated by retinoic acid. The increase of intracellular Ca2+ induced by the partial depolarization of the plasma membrane with KCl down-regulated both the basal and the cAMP-stimulated transcription. The down-regulation of the latter may be mediated by the phosphorylation of the CRE-binding protein by a calmodulin-dependent kinase (CaMKII). The exposure of cells to BDNF after treatment with retinoic acid rapidly induced promoter activity during the initial five hours and phosphorylation of CRE-binding protein during the first two hours. The promoter activity was further enhanced by cAMP, but became insensitive to Ca2+. In BDNF-stimulated cells cAMP elevation caused the preferential phosphorylation of ATF1 instead of that of CRE-binding protein.

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Transcriptional regulation by cAMP and Ca2+ links the na+/ca2+ exchanger 3 to memory and sensory pathways.

Gabellini N.

Department of Biological Chemistry, University of Padova, Padova, Italy.

The signaling cascades triggered by neurotrophins such as BDNF and by several neurotransmitters and hormones lead to the rapid induction of gene transcription by increasing the intracellular concentration of cAMP and Ca2+. This review examines the mechanisms by which these second messengers control transcriptional initiation at CRE promoters via transcription factor CREB, as well as at DRE sites via transcriptional repressor DREAM. The regulation of the SLC8A3 gene encoding the Na+/Ca2+ exchanger 3 (NCX3) is taken as an example to illustrate both mechanisms since it includes a CRE site in the promoter and several DRE sites in the exon 1 sequence. The upregulation of the NCX3 by Ca2+ signals may be specifically required to establish the Ca2+ balance that regulates several physiological and pathological processes in neurons. The regulatory features and the expression pattern of SLC8A3 gene suggest that NCX3 activity could be crucial in neuronal functions such as memory formation and sensory processing.

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